REMARKS

Applicants wish to thank the Examiner for withdrawing the requirement of an IL-21/IL-21R species election.

Claims 1-19 and 29-40 are currently pending and under examination in this application. Claims 1, 17, 29 and 35 have been amended in response to the Examiner's enablement rejection. Support for these amendments can be found in the specification, e.g., at paragraphs [0005] and [0025]. Claims 5 and 6 have been amended to correct typographical errors. Claims 1, 17, 29, 34 and 35 have been amended to recite the method of treating, preventing, or ameliorating a disorder or a symptom of a disorder associated with an IL-10 deficiency in a subject. Support for these amendments can be found in the specification, e.g., at paragraphs [0007], [0027]-[0028], [0125] and [0149]. Claims 1 and 29 have been amended to include a method of treating, preventing, or ameliorating multiple sclerosis or a symptom of multiple sclerosis associated with the modulation of the cytokines listed in Table 3. Claim 8 has been amended in accordance with the response to the restriction requirement. Claim 14 has been amended to correct a typographical error. Claims 16-19 have been amended to correct the claim language and more fully describe the subject matter of these claims. Claim 34 has been amended in response to the indefiniteness rejection; support for this amendment can be found in the specification, e.g., at paragraphs [0007], [0027]-[0028] and [0125]. Claim 40 has also been amended in response to the indefiniteness rejection; support for this amendment can be found in the specification, e.g., at paragraph [0126]. Consequently, no new matter has been added by the way of these amendments. Consideration of the amendments and remarks included herein is respectfully requested.

Applicants presently amend paragraphs [0038] and [0068] in the specification. In paragraph [0038], Applicants substitute the attorney docket number and the title of the PCT Patent Application with the presently known PCT Patent Application Number. No new matter has been added by the way of this amendment.

In paragraph [0068], Applicants correct a typographical error in the GenBank Accession No. As indicated in the "Sample GenBank Record instructions" (submitted herewith as a part of an Information Disclosure Statement (IDS)), at page 8 of 17, records from RefSeq sequence database have accession numbers that begin with two letters followed by an underscore bar and six or more digits. The Accession Format in "RefSeq instructions" (submitted herewith as a part of an IDS), at page 2 of 7, indicates that accession numbers beginning with "XM_" correspond to nucleic acid molecules and accession numbers beginning with "XP_" correspond to protein molecules. Thus, one skilled in the art would realize that the omissions of the capital letter M or the capital letter P in the accession number of human IL-21 is a typographical error, and no new matter has been added by the way of this amendment. Indeed, a search for GenBank accession number XM_011082 reveals human IL-21 nucleic acid molecule, and a search for GenBank accession number XP_011082 reveals human IL-21 protein molecule (records submitted herewith as a part of an IDS).

Enablement rejection under 35 U.S.C. § 112, first paragraph

The Examiner states that the specification does not enable claims 1-19 and 29-40 because the specification allegedly does not provide enablement for preventing immunological disorders by administering to a subject an agonist of IL-21/IL-21R as

claimed; ameliorating all symptoms of multiple sclerosis (MS); and modulating other disorders associated with an IL-10 deficiency (*Office Action*, page 3). More specifically, the Examiner alleges that the specification does not enable: (1) using any agonistic IL-21R antibody to increase IL-10 and decrease IFN-γ; (2) using an agonistic IL-21 polypeptide that comprises an amino acid sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO:2 to increase IL-10 and decrease IFN-γ ; (3) ameliorating all symptoms of MS in patients; (4) using IL-21 antagonists to modulate all disorders associated with an IL-10 deficiency; (5) using nonhuman antibodies to treat or prevent human disease; and (6) evaluating whether a subject is at risk for developing MS by evaluating an IL-10 parameter (*Office Action,* pages 5-10). For the following reasons, Applicants respectfully disagree.

A. Legal standard for enablement

To satisfy 35 U.S.C. § 112, an applicant must disclose an amount sufficient to allow one skilled in the art to practice the invention without undue experimentation (see *In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991)). However, that some experimentation (or even extensive experimentation) is required to practice a claimed invention does not necessarily invalidate a claim under § 112 (see *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (stating "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed")). Therefore, "[e]nablement is not precluded by the necessity for some experimentation... 'The key word is 'undue,' not 'experimentation.'" *In re Wands*, 858 F.2d at 736-7 (quoting, *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A 1974)). Accordingly,

trial-and-error may be acceptable and will not render a claim invalid if the experimentation is routine or the specification provides a reasonable amount of guidance (see *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) ("That some experimentation may be required is not fatal...")).

B. Applicants' arguments

(1) Agonistic IL-21R antibodies

The Examiner acknowledges that the specification is enabling for increasing the levels of IL-10 and decreasing secretion of IFN-γ and the other cytokines listed in Table 3 *in vitro* and *in vivo* with the IL-21 polypeptide of SEQ ID NO:2, and thus is enabling for reducing symptoms regulated by IFN-γ, IL-10 and the other cytokines listed in Table 3 by administering IL-21 to patients (*Office Action*, pages 4-5).[1] Thus, Applicants have amended claims 1 and 29 to include all cytokines that the Examiner believes are enabled. However, the Examiner alleges that the specification does not provide sufficient guidance regarding whether administration of any agonist IL-21R antibody would similarly result in increasing IL-10 and decreasing IFN-γ (*Office Action*, page 5). For the following reasons, Applicants respectfully disagree.

The Examiner cites Ledbetter et al. ((1995) *Circ. Shock* 44:67-72) in support of the allegation that the mechanism of activation by agonistic antibodies is different from other antibodies (e.g., antagonistic or neutralizing antibodies) (*Office Action*, page 5). Applicants believe the Examiner cites Ledbetter et al. to suggest that some antibodies act as partial agonists, not full agonists (because Ledbetter et al. shows

[1] Applicants note that, although the Examiner states that Applicants are enabled for reducing symptoms regulated by IL-10 by administering IL-21 to patients, the Examiner alleges that one skilled in the art cannot apply the findings from the EAE mouse model (e.g., that IL-21 can induce IL-10 secretion) to human subjects (*Office Action*, pages 6-7). For this reason, Applicants respectfully request that the Examiner clarify the Examiner's belief as to what is and is not enabled.

that the G28-5 antibody against the CD40 receptor acts as a partial agonist).[2] Applicants note that the present method claims specifically recite agonistic IL-21R antibodies (see, e.g., claim 1). Thus, although certain IL-21R antibodies may act as antagonists, such antibodies are not within the scope of the presently claimed methods. Further, any agonistic antibody, whether a full or partial agonist, is within the scope of the claims as long as that antibody treats, prevents, or ameliorates multiple sclerosis (MS) or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18; or an immunological disorder associated with an IL-10 deficiency. Accordingly, regardless of the strength of the agonistic IL-21R antibody, the result must be as claimed, and therefore sufficient guidance has been given for the use of such antibodies.

As defined by Merriam-Webster Online Dictionary, an agonist is "a chemical substance capable of combining with a specific receptor on a cell and initiating the same reaction or activity typically produced by the binding endogenous substance" (emphasis added; see, "Definition of agonist," submitted herewith as a part of an IDS). Therefore, Applicants submit that it is predictable that an agonistic IL-21R antibody would initiate the same reaction or activity as typically produced by the IL-21 cytokine. Given the teachings in the specification and the level of knowledge held by those skilled in the art, a skilled artisan would be able to make and use agonistic antibodies to IL-21R that achieve the claimed results. For example, Applicants teach how to make polyclonal and monoclonal antibodies to IL-21R (*Specification*, at paragraphs [0100]-[0102]). Additionally, one skilled in the art would know how to test whether these antibodies bind

[2] Applicants respectfully ask the Examiner to kindly confirm that their understanding of the use of Ledbetter et al. in this rejection is accurate.

IL-21R (by using, e.g., a well-known ELISA assay). Thus, making antibodies against IL-21R does not require undue experimentation. One skilled in the art would also know how to test whether an antibody to IL-21R is an agonistic antibody. For example, a skilled artisan would know to use, e.g., the experimental protocol of the example section entitled "Proliferative response and cytokine production induced by murine IL-21" on pages 49-51 to culture lymphocytes with an IL-21R antibody and determine whether the antibody is capable of inducing the same reaction or activity typically produced by IL-21. Thus, determining whether an anti-IL-21R antibody is an agonist does not require undue experimentation. Therefore, Applicants respectfully submit that any experimentation required to determine whether an anti-IL-21R antibody is agonistic is not undue, and requires mere routine trial and error.

Upon successful generation of an agonistic anti-IL-21R antibody, one of skill in the art would be able to use the experiments disclosed in the specification, particularly the mouse EAE studies, to determine whether the agonistic anti-IL-21R antibody would be capable of modulating the cytokines in Table 3 of the specification, e.g., increasing IL-10 and/or decreasing IFN-γ in a subject. Thus, determining whether an agonistic IL-21R antibody is capable of treating, preventing, or ameliorating MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18; or an immunological disorder associated with an IL-10 deficiency, does not require undue experimentation.

(2) Agonistic IL-21 polypeptide

The Examiner alleges that Applicants do not enable the use of an agonistic IL-21 polypeptide that comprises an amino acid sequence at least 90% identical to an

amino acid sequence of SEQ ID NO:2 (i.e., human IL-21) and that is capable of binding to an IL-21R to ameliorate MS (*Office Action*, page 5). For the following reasons, Applicants respectfully disagree.

Applicants submit that one skilled in the art would be able to combine the teachings of the specification and the knowledge generally available in the art to determine whether an agonistic IL-21 polypeptide that comprises a sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2 (i.e., IL-21) would be capable of treating, preventing, or ameliorating MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18; or an immunological disorder associated with an IL-10 deficiency. The claims indicate that an IL-21 polypeptide that is at least 90% identical to SEQ ID NO:2 must be agonistic; therefore, the claims exclude any IL-21 polypeptide that does not satisfy this limitation. One skilled in the art can easily determine: (i) the percent identity of a polypeptide to SEQ ID NO:2; (ii) residues of IL-21 that should not be significantly altered in order to retain activity; and (iii) whether an IL-21 polypeptide with at least 90% identity to SEQ ID NO:2 acts as an agonist. For example, percent identity can be determined as described in specification at paragraphs [0062]-[0063]. The specification also teaches that IL-21 agonists may have conservative amino acid substitutions, which would not be expected by one of ordinary skill in the art to have a substantial effect on IL-21 function (*Specification*, at paragraph [0065]). One skilled in the art would be able to align the available sequences of IL-21 from different species,[3] or the sequences of human IL-21 to the sequences of closely related cytokines (e.g., IL-2, IL-15, etc.) to

[3] For example, the "Amino Acid Sequence Alignment of Mature Human and Mouse IL-21" (submitted herewith as a part of an IDS), or a related alignment, may be used by one of ordinary skill in the art in determining which residues of IL-21 may be altered without substantially affecting IL-21 function.

determine residues that can be replaced without significantly affecting activity. One skilled in the art would also know how to generate an IL-21 polypeptide comprising a sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2, e.g., using the well-known method of site-directed mutagenesis (see, e.g., § 20-3 (pp. 738-44) in Basic Methods in Molecular Biology, 2nd Edition (1994) Davis et al. (Eds.) Appleton & Lange, CT; submitted herewith as part of an IDS). Additionally, one skilled in the art would know to use assays taught in the specification (e.g., the assays presented in the example sections entitled "Proliferative response and cytokine production induced by murine IL-21" (at pages 49-51) and "Development of EAE in mice treated with IL-21" (at pages 51-52) to determine whether an IL-21 that comprises a sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO:2 retains the ability to treat, prevent, or ameliorate MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18; or an immunological disorder associated with an IL-10 deficiency. Therefore, Applicants respectfully submit that no undue experimentation is required to determine whether an agonistic IL-21 polypeptide that comprises a sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO:2 is capable of treating, preventing, or ameliorating MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18; or an immunological disorder associated with an IL-10 deficiency.

(3) Ameliorating symptoms of MS in patients

The Examiner alleges that the Applicants have not enabled ameliorating all symptoms of MS as recited in claim 1 (*Office Action*, pages 5–6). The Examiner

contends that MS pathology is very heterogeneous and the effects shown in one MS model do not reflect the results in MS patients (*Office Action*, page 6). The Examiner concludes that the success of administering an IL-21 agonist for treating, preventing, or ameliorating MS or symptoms of MS is unpredictable. Therefore, the Examiner believes that the Applicants have not provided guidance in applying the findings from the mouse models used in the specification to treating MS (*Office Action*, page 7). For the following reasons, Applicants respectfully disagree.

Applicants have amended the claims to recite a method of treating, preventing, or ameliorating MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18; or an immunological disorder associated with an IL-10 deficiency in a subject. Applicants also submit that demonstrating a successful treatment in the mouse MS model with an IL-21 agonist is sufficient to enable methods of treating, preventing, or ameliorating MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18; or an immunological disorder associated with an IL-10 deficiency.

MPEP § 2164.2 states "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating with the condition" (MPEP §2164.02, citing *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995)). However, a rigorous or an invariable exact correlation of a model to a claim is not

required as long as the disclosure of pharmacological activity is reasonable. *Cross v. Iizuka,* 753 F.2d 1040, 1050 (Fed. Cir. 1985). Thus, Applicants need only show that the mouse MS model reasonably correlates with the claimed methods.

The 't Hart manuscript cited by the Examiner on page 6 of the Office Action states that "rodent models of MS have been critical for the study of the basic mechanisms of recruitment of inflammation within the CNS as well as mechanisms leading to myelin and axonal damage. These studies have formed the basis for the development of therapeutic strategies..." (t'Hart, page 379, left column, third paragraph (emphasis added)). As indicated in a recent review by Steinman and Zamvil ((2006) *Ann. Neurol.* 60:12-21; submitted herewith as a part of an IDS), the EAE animal model has directly led to the development of three current therapies for MS, and has proven useful in aiding MS research in general (see, e.g., abstract). Thus, one of ordinary skill in the art would accept that Applicants' findings in the MS mouse model reasonably correlate with Applicants' method claims.

In addition, Applicants are not required to demonstrate therapeutic efficacy of IL-21 agonists using human subjects in order to enable methods of treating, preventing, or ameliorating MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18; or an immunological disorder associated with an IL-10 deficiency. Utility for a therapeutic invention may be found despite the fact that an applicant is at an early stage in the development of a pharmaceutical product. *Cross v. Iizuka,* 753 F.2d at 1051. The enablement standard does not require FDA approval for claims such as those Applicants present herein. See *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) (stating that

"[t]esting for full safety and effectiveness of a prosthetic device is more properly left to the [FDA]"); MPEP § 2164.05). The stage at which a therapeutic invention becomes useful is well before that invention is ready to be administered to a human. *In re Brana*, 51 F.2d 1560. Thus, Applicants are not required to show successful results in humans, and instead have used a model that one of ordinary skill in the art would accept as reasonably correlating to the claimed methods.

(4) Modulating disorders associated with an IL-10 deficiency

Applicants respectfully submit that they have also taught one of ordinary skill in the art how to treat, prevent, or ameliorate other disorders associated with an IL-10 deficiency, and that no undue experimentation is required to perform these methods. For example, Applicants teach a variety of disorders that are associated with an IL-10 deficiency (e.g., *Specification*, at paragraph [0026]). Applicants also teach one of ordinary skill in the art how to measure changes in cytokine levels in a sample or subject (e.g., by measuring mRNA levels or protein levels using, e.g., ELISA; *Specification,* at paragraphs [0145]-[0147]). The specification also teaches that the IL-10 levels in a subject can be measured and compared to the IL-10 levels in a normal subject (*Specification*, at paragraphs [0026] and [0149])). Thus, one of ordinary skill in the art would know to measure cytokine levels in a patient and determine whether an immunological disorder is associated with an IL-10 deficiency, and subsequently evaluate the efficacy of IL-21 treatment.

(5) Nonhuman antibodies to IL-21

The Examiner also alleges that Applicants have not provided guidance for using nonhuman antibodies to "treat/prevent the disease" (*Office Action*, page 9, lines 10-17). For the following reasons, Applicants respectfully traverse this rejection.

Applicants note that the independent claims are not directed solely to human subjects, but rather are directed to treating, preventing, or ameliorating a symptom of MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18; or an immunological disorder associated with an IL-10 deficiency, in "a subject." Dependent claim 30 is directed to a human subject, but recites a method of treating, preventing, or ameliorating MS by administering an IL-21 polypeptide, not an anti-IL-21 antibody. The claims that do recite an agonistic anti-IL-21R antibody encompass, *inter alia*, using a nonhuman agonistic IL-21 antibody (except dependent claim 6). However, one skilled in the art would recognize that if the subject is a human, then desirable antibodies might include, e.g., human antibodies, humanized antibodies, chimeric antibodies, etc. The specification describes the methodology for generating both humanized antibodies and chimeric antibodies, and provides the references describing such methods (*Specification*, at paragraphs [0103]-[0105]). Further, many humanized and chimeric antibodies for the treatment of human diseases have been successfully developed and gained approval in both the United States and the European Union (see, e.g., Reichert and Pavlou (2004) *Nat. Rev. Drug Discovery* 3:382-84, particularly Table 1; submitted herewith as a part of an IDS). Therefore, one skilled in the art would know how to modify an antibody for use in human subjects. Thus, Applicants submit that no undue experimentation is required to

use agonistic IL-21 antibodies to treat, prevent, and/or ameliorate MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18; or an immunological disorder associated with an IL-10 deficiency.

(6) Evaluating a subject at risk for developing MS

The Examiner has rejected claims 16-19, alleging that one skilled in the art would not be able to identify whether the subject is at risk of MS by evaluating IL-10 (*Office Action*, pages 8-9). For the following reasons, Applicants respectfully disagree.

Claim 16 depends on claim 1, which has been amended to include a method of preventing MS in a subject. Applicants submit that the method of preventing MS by evaluating the IL-10 parameter is enabled. For example, Applicants describe that MS is associated with an IL-10 deficiency (*Specification*, at paragraph [0005]). Applicants also describe that an IL-10 deficiency is a statistically significant decrease in IL-10 relative to a corresponding normal subject (*id.*, at paragraph [0025]). Applicants also teach that evaluating whether a subject is at risk of developing MS includes evaluating an IL-10 parameter (*id.*, at paragraph [0015]). Although the Examiner contends that many immunological diseases are associated with an IL-10 deficiency, Applicants submit that one skilled in the art would recognize from the teachings of the instant application that a decrease in an IL-10 parameter in a subject relative to the normal subject puts the former subject at risk of developing MS, regardless of any other diseases for which the subject may also be at risk. Once the subject is determined to be at risk for MS (e.g., determined to have decreased IL-10 parameter), he/she may be treated to prevent MS. Thus, Applicants submit that they have enabled a method of evaluating a

subject for risk of developing MS, as well as treating, preventing, or ameliorating MS in such a subject.

For at least the reasons set forth above, Applicants respectfully submit that claims 1-19 and 29-40 satisfy the enablement requirement of 35 U.S.C. § 112, and therefore respectfully request withdrawal of the enablement-based rejections of claims 1-19 and 29-40.

Written description rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-3, 29-30, and 34-40 as allegedly reciting subject matter that is not adequately described (*Office Action*, pages 10-13). The Examiner alleges that the specification does not provide an adequate written description of a genus of IL-21 polypeptides that comprise a sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2 and that are capable of binding to an IL-21R. For the following reasons, Applicants respectfully disagree.

A. Legal standard for written description

The purpose of the written description requirement is to ensure that the applicant possessed the claimed invention at the time of the filing. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956 (Fed. Cir. 2002). For chemical compounds such as genes or proteins, an applicant must disclose sufficient identifying characteristics so one of skill can "visualize or recognize the identity" of the invention. *Regents of the University of California v. Eli Lilly, Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). For generic claims, the specification must describe "species sufficient to constitute the genera." *Enzo*, 323 F.3d at 967. The MPEP §2163 states that addressing the written description requirement for a genus requires the analysis of several factors.

> Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the methods of making the claimed invention. See *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406.

B. Applicants' arguments

Applicants submit that they have adequately described a genus of IL-21 polypeptides that comprise a sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2. The present invention presents two exemplary sequences of IL-21 polypeptides, human (SEQ ID NO:2) and mouse (SEQ ID NO:4). SEQ ID NO:2 and SEQ ID NO:4 share approximately 61% identity (see "Amino Acid Sequence Alignment of Mature Human and Mouse IL-21," submitted herewith as a part of an IDS). Therefore, Applicants have described two IL-21 polypeptides that share less than 90% identity.

The claims, as currently presented, require the IL-21 polypeptides to be those that comprise a sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2 (human IL-21), and which also bind an IL-21 receptor ("IL-21R"). Thus, Applicants have described the recited genus by providing exemplary sequences and functionality. Therefore, Applicants submit that they have sufficiently described the IL-21 polypeptide genus used in the claimed methods.

Applicants also believe that one skilled in the art would recognize that, at the time of filing, they possessed a genus of IL-21 polypeptides that comprise a sequence at least 90% identical to the amino acid sequence of SEQ ID NO:2, which are also capable of binding the IL-21R. At the time of filing, one skilled in the art would recognize, based on the disclosed IL-21 sequences and the knowledge available in the art

regarding cytokine receptor-ligand interactions, that alignment of IL-21 polypeptide sequences from different species (e.g., mouse and human) and alignment of IL-21 polypeptide sequences with polypeptide sequences of other interleukin cytokines (e.g., IL-2) would indicate regions of IL-21 responsible for activity. One of skill in the art would know that alterations of the conserved regions may reduce IL-21 activity, e.g., receptor binding, and that these residues should not be significantly altered (e.g., in order for a variant IL-21 to retain receptor-binding capacity).

As nonlimiting examples, one of skill in the art could compare and align the sequences of GenBank Accession Nos. XP_011082 and NP_068554 (submitted herewith as a part of an IDS), or use the aforementioned "Amino Acid Sequence Alignment of Mature Human and Mouse IL-21," to identify IL-21s within the scope of the instant claims, and thus would recognize and accept that Applicants possessed the recited genus. Based on alignments such as these, one of skill in the art would know which amino acids should not be altered in order to preserve activity, e.g., receptor binding. As well as alignments, one of ordinary skill in the art could identify regions of IL-21 amenable (or not amenable) to substitution by reviewing publications available before the earliest priority date. For example, Brandt et al. ((2001) *J. Leukoc. Biol. (Suppl.)* 46 (Abstr. 119); submitted herewith as a part of an IDS) suggest that amino acid substitutions in the D-helix of IL-21 can inhibit cellular signaling; therefore, one skilled in the art would know not to significantly alter amino acids in the D-helix of IL-21 in order to retain IL-21 signaling activity. Thus, one skilled in the art would recognize that Applicants possessed a genus of IL-21 polypeptides comprising a sequence with at least

90% identity to the amino acid sequence of SEQ ID NO:2 that is capable of binding IL-21R.

In addition to the disclosure of the specification and the knowledge available to one of ordinary skill in the art regarding physical / chemical and structural properties of IL-21, Applicants describe the functional properties of the IL-21 polypeptide genus recited in the method claims. For example, Applicants demonstrate that IL-21 causes increased proliferation of T cells, induces secretion of the Th2 cytokine, IL-10, and decreases the level of IFN-γ (*Specification*, at paragraphs [0177]-[0181]). As these functions are mediated by the IL-21 ligand binding to the IL-21R, and binding is explicitly noted as a claim limitation, Applicants have functionally characterized the recited genus.

In summary, Applicants submit that the level of skill and knowledge available in the art, coupled with the disclosure of human and mouse IL-21 sequences in the specification and the functional characterization of the IL-21 cytokine genus in the examples, adequately describes a genus of IL-21 polypeptides that comprise sequences at least 90% identical to the amino acid sequence of SEQ ID NO:2 that are capable of binding to an IL-21R. For at least these reasons, Applicants respectfully request withdrawal of the written description-based rejection of the claims.

Indefiniteness rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1,[4] 16-19, and 34-40 under 35 U.S.C. § 112, as allegedly being indefinite. For the following reasons, those rejections are respectfully traversed.

The Examiner alleges that the specification does not adequately define "an IL-10 parameter," and fails to set forth the metes and bounds of what is encompassed within the definition of "an IL-10 parameter" (*Office Action*, page 14). However, the specification clearly describes "IL-10 parameter" at paragraphs [0014] and [0028], including how and when it should be measured. Therefore, Applicants submit that the phrase "IL-10 parameter" satisfies the definiteness requirement of 35 U.S.C. § 112. (See *Shatterproof Glass Corp. v. Libbey-Owens Ford, Co.,* 758 F.2d 613, 624 (Fed. Cir. 1985) (stating that claim language need only reasonably apprise one of skill in the art of the claim boundaries in order to satisfy the definiteness requirement of 35 U.S.C. § 112)).

The Examiner alleges that the specification does not define the term "disorder associated with an IL-10 deficiency" (*Office Action*, page 14). However, the specification indicates that an IL-10 deficiency is a "statistically significant decrease in IL-10 relative to a corresponding normal subject" (*Specification*, at paragraph [0025]). The specification also describes how IL-10 levels can be monitored, and lists several exemplary disorders associated with an IL-10 deficiency (*Specification*, at paragraph [0026]). Therefore, Applicants submit that they have defined the phrase "disorder associated with an IL-10 deficiency" in accordance with 35 U.S.C. § 112, second paragraph.

[4] Applicants note that claim 1 is mentioned at the beginning of the Examiner's comments regarding indefiniteness, (Office Action, p. 14), but no specific phrase is addressed in claim 1.

The Examiner also alleges that Applicants have not defined the term "activity," as it is used in the phrase "IL-10 activity" (*Office Action*, page 14). Applicants respectfully disagree. According to MPEP §2173, definiteness of claim language must be analyzed in light of: (a) the content of the application disclosure; (b) the teachings of the prior art; and (c) the claim interpretation that would be given to terms by one of ordinary skill in the art at the time the invention was made. "[T]he examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope." (*Id.)* Accordingly, the phrase "IL-10 activity" is definite if one skilled in the art understands its meaning as used in the claims. Applicants submit that a skilled artisan would instantly know that "IL-10 activity" is used to refer to IL-10 protein activity. The specification discloses at least one IL-10 protein activity, e.g., the ability of IL-10 to regulate MS symptoms (*Specification*, at paragraph [0005]). In addition, at the time of filing of the application, various other IL-10 activities were known in the art (see, e.g., Smith et al. (1999) *J. Neuroimmunol.* 100:140-48, submitted herewith as a part of an IDS). Thus, Applicants respectfully submit that the phrase "IL-10 activity" is definite within the meaning of 35 U.S.C. § 112, second paragraph.

The Examiner also alleges that Applicants have not defined what is encompassed within the definitions of "modulation" and "alteration" as used in claims 34 and 40 (*Office Action*, pages 14–15). Applicants have amended claim 34 to recite a method of "treating, preventing, or ameliorating" an IL-10 deficiency. Support for this amendment can be found in the specification at [0007], [0025] and [0027]-[0028]. Applicants have amended claim 40 to recite that the immunological disorder "is characterized by damage, degradation, or loss of myelin sheaths." Support for this

amendment can be found in the specification at [0126]. In addition, at the time of filing of the instant application, one of ordinary skill in the art would know that MS and several other immunological disorders were characterized by damage, degradation, or loss of myelin sheath (see, e.g., Bjartmar et al. (1999) *J. Neurocytol.* 28:383-95; submitted herewith as part of an IDS). Therefore, Applicants believe that these amendments satisfy the Examiner's concerns relative to claims 34 and 40.

Because Applicants have either amended the instant claims or have demonstrated how the instant claims satisfy the definiteness requirement of 35 U.S.C. § 112, second paragraph, Applicants respectfully request withdrawal of the outstanding indefiniteness-based rejections of claims 1, 16-19 and 34-40.

Rejection under 35 U.S.C. § 102(e)

The Examiner rejected claims 1-4, 9-12, 14 and 29-34 under 35 U.S.C. § 102 as anticipated by U.S. Patent No. 6,605,272 ("the '272 patent") (*Office Action*, pages 15-17). For the following reasons, Applicants respectfully traverse the rejection.

It is without question that a reference must teach every element of a claim in order to anticipate that claim. *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990); see also MPEP §2131. The Examiner bears the burden of demonstrating that a reference teaches every element of a claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Thus, to anticipate claims 1-4, 9-12, 14 and 29-34, the Examiner must show that the '272 patent teaches that IL-21 agonists are useful in treating, preventing, or ameliorating MS or a symptom of MS associated with an IL-10

deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18; and a disorder associated with an IL-10 deficiency.

The Examiner alleges that the '272 patent teaches administration of IL-21 for treating several immunological disorders, e.g., MS, and for enhancing an immune response (*Office Action*, pages 15-17). However, MS is largely considered a T helper (Th)1-driven autoimmune disorder; thus, antagonism of Th1 cells and/or Th1-associated cytokines (for example, IL-18 and IFN-γ are often classified as Th1-associated cytokines), and agonism of Th2 cells and/or Th2-associated cytokines, is believed to be useful to treat MS. The '272 patent merely suggests that IL-21 mediates its effects through regulation of B cells and NK cells (the '272 patent, at column 39) – cells with unclear roles in MS – and the '272 patent does not indicate that IL-21 even modulates Th cells. Thus, the '272 patent fails to provide any information regarding whether IL-21 antagonizes a Th1 response, or whether IL-21 agonizes a Th2 response. Without knowing how IL-21 regulates Th cells, the '272 patent cannot convey whether one should stimulate or abrogate IL-21 signal to successfully treat MS or a symptom of MS, i.e., whether one should use an IL-21 agonist or an IL-21 antagonist. Accordingly, the '272 patent lacks the limitation "administering to the subject an agonist of an interleukin-21 (IL-21)/IL-21 receptor (IL-21R)" as recited in claims 1-4, 9-12 and 14, and the limitation "administering to the subject an agonistic interleukin-21 (IL-21) polypeptide" as recited in claims 29-33. In addition, as amended, claims 1-4, 9-12, 14 and 29-33 require MS or a symptom of MS to be associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18. The '272 patent does not teach an association between IL-21, IL-10 and MS or a symptom of MS, and therefore cannot

teach that an IL-21 agonist is useful to treat MS or a symptom of MS associated with IL-10. Likewise, the '272 patent does not teach an association between the other cytokines listed in Table 3 (e.g., IFN-γ, IL-1α, IL-2, IL-6, IL-18), IL-21, and MS or a symptom of MS. Accordingly, the '272 patent does not contain all the limitations of claims 1-4, 9-12, 14 and 29-33, and therefore cannot anticipate the claims.

In addition, the '272 patent does not teach a method of treating, preventing, or ameliorating an IL-10 deficiency by administering IL-21, as recited in claim 34. The '272 patent does not teach a link between IL-21 and IL-10, or that IL-21 administration increases IL-10 levels. Thus, because the '272 patent lacks this limitation of claim 34, it cannot anticipate claim 34.

Further, the '272 patent admits that several diseases, including MS, "are the result of a complex network of immune dysfunction ... and that immune cells are dependent upon interaction with one another to elicit a potent immune response" ('272 patent, column 42, lines 23-27). The '272 patent further states (column 42, lines 29-31) that IL-21 is "an attractive therapeutic candidate for intervention at multiple stages of disease" (apparently referring to the "wide range of diseases arising from defects in the immune system" noted at column 42, lines 19-20 of the '272 patent). Therefore, although the '272 patent states that IL-21 may be useful to treat MS, it does not teach one how to use IL-21 to treat MS or symptoms of MS (i.e., whether one should agonize or antagonize IL-21 to treat MS or the symptoms of MS). As art used for the purpose of anticipation must be enabling, and because the '272 patent is not enabling for Applicants' method claims, Applicants respectfully submit that the '272 patent cannot anticipate Applicants' claimed method.

For at least these reasons, Applicants respectfully request withdrawal of the anticipation-based rejection of claims 1-4, 9-12, 14 and 29-34.

Rejection under 35 U.S.C. § 103

A. Rejection under 35 U.S.C. § 103(a) over the '272 patent in view of U.S. Patent Application Publication No. 2003/0108549 and Kawai

The Examiner has rejected claims 1-15 and 29-33 under 35 U.S.C. § 103(a) as allegedly obvious over the '272 patent in view of U.S. Patent Application Publication No. 2003/0108549 ("the '549 application") and Kawai et al. (1996) *Cell Immunol.* 171:262-68 ("Kawai") (*Office Action*, pages 17-20). For the following reasons, Applicants respectfully traverse this rejection.

According to *Graham v. John Deere*, the nonobviousness statutory requirement requires a comparison between the prior art and the elements of a claimed invention. 383 U.S. 1 (1966). Only if: 1) a combination of prior art references contains all the elements of a claimed invention, and 2) one of ordinary skill in the art would have found the invention as a whole to be obvious in light of those references at the time the invention was made, is a claimed invention obvious under 35 U.S.C. §103. *Id.* Such a combination will establish *prima facie* obviousness of claimed invention if there is a motivation or suggestion to combine the references and there exists a reasonable expectation of success of arriving at the claimed invention. *In re Vaeck,* 947 F.2d 488 (Fed. Cir. 1991); MPEP § 2142. The teaching of a reasonable expectation of success must be found in the cited art rather than in an applicant's disclosure. *Id.* The motivation to combine references or the suggestion to modify a reference may be found in the nature

of the problem to be solved, the teachings of the prior art, or the common knowledge of persons of skill in the art. *In re Rouffet,* 149 F.3d 1350 (Fed. Cir. 1998).

The Examiner alleges that the '272 patent teaches all the limitations of claims 1, 5-6, 7-8 and 13-15, but fails to teach an agonistic anti-IL-21R antibody (as recited in claims 1, 5 and 6); an anti-inflammatory agent (as recited in claims 7-8); and administration routes (as recited in claims 13-15) (*Office Action*, at page 18). The Examiner also alleges that the '549 application teaches an IL-21 polypeptide and an agonistic antibody to IL-21R, as well as combining an IL-21 agonist and an anti-inflammatory agent to treat T cell-mediated diseases (*id.)*. Thus, the Examiner contends that a combination of the '272 patent and the '549 application provides motivation to use a composition comprising IL-21 and an anti-inflammatory agent to treat MS (*id.)*. In addition, the Examiner alleges that Kawai teaches intracerebroventricular and intrathecal routes of administration, which allegedly fall within methods of administering IL-21 agonists as in claims 13-15 (*id.)*. Thus, the Examiner alleges that the combination of the '272 patent, the '549 application, and Kawai provides motivation and an expectation of success in delivering agents to the EAE rat model by intrathecal administration (*id.)*. For the following reasons, Applicants respectfully disagree with this assertion.

As discussed above, the '272 patent does not teach treating, preventing, or ameliorating MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18, by using IL-21 agonist. The '272 patent also does not provide a link between IL-21 and an IFN-γ, IL-1α, IL-2, IL-6, or IL-18 decrease; or IL-21 and IL-10 production. The '272 patent

also does not teach an agonistic anti-IL-21R antibody or administering a combination comprising an agonistic anti-IL-21R antibody or other IL-21 agonist with an anti-inflammatory agent.

The '549 application does not rescue the deficiencies of the '272 patent. Like the '272 patent, the '549 application does not teach the role of IL-21 in modulating Th cells, and does not teach the role of IL-21 or IL-21 agonists in treating MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18. In fact, the '549 application teaches the administration of an IL-21 antagonist to treat, e.g., MS (see the '549 application at [0008], [0189] and [0208]). Accordingly, the '549 application, when considered as a whole, teaches away from Applicants' invention, because Applicants' invention requires the use of an IL-21 agonist. Furthermore, as the '549 application proposes using an IL-21 antagonist, one skilled in the art would lack a reasonable expectation of success of arriving at Applicants' invention.

Kawai et al. does not overcome the deficiencies of the '272 patent and the '549 application. Although Kawai teaches intracerebroventricular and intrathecal administration routes of compounds for use in the EAE model, Kawai does not teach administration of an IL-21 agonist to treat MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18.

In sum, as described above, the references cited by the Examiner lack a variety of the limitations found in claims 1-15 and 29-33. When combined, the '272 patent, the '549 application, and Kawai lack the limitations of: (1) using an IL-21 agonist;

and (2) treating, preventing, or ameliorating MS or symptoms of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18. Further, upon combination of these references, the '549 application suggests that one would use an IL-21 antagonist to treat MS, which teaches away from Applicants' inventive methods, and which indicates that one of ordinary skill in the art would not have a reasonable expectation of success in arriving at Applicants' methods.

Furthermore, as the '549 application suggests using an IL-21 antagonist, Applicants respectfully submit that their finding that one may use an IL-21 agonist to treat MS or a symptoms of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18, is a surprising and unexpected result sufficient to overcome any *prima facie* obviousness.

For at least these reasons, Applicants respectfully submit that a combination of the '272 patent, the '549 application, and Kawai does not disclose or suggest the subject matter of the claims 1-15 and 29-33. Accordingly, Applicants respectfully request withdrawal of the outstanding obviousness-based rejections of claims 1-15 and 29-33.

B. Rejection 35 U.S.C § 103(a) over the '272 patent in view of the '549 application and Kawai, further in view of Beebe

The Examiner has rejected claims 1-19 and 29-40 under 35 U.S.C. §103(a) over the '272 patent, the '549 application, and Kawai, further in view of Beebe et al. (2002) *Cytokine Growth Factor Rev.* 13:403-12 ("Beebe") (*Office Action*, pages 20-21). The Examiner alleges that Beebe overcomes the deficiency in the combination of the '272 patent, the '549 application, and Kawai because Beebe teaches evaluating the level

of IL-10 in MS patients. For the following reasons, Applicants respectfully traverse this rejection.

Beebe teaches an association of increased IL-10 with treatment of MS. However, Beebe does not provide any association between IL-21 agonism and IL-10 levels, which, as discussed above, is also lacking from the combination of the '272 patent, the '549 application, and Kawai. Without knowing that IL-21-based MS treatment increases IL-10 levels, one would not be prompted to: (1) use IL-21 to treat MS or a symptom of MS (claims 1-15); or (2) measure an increase in IL-10 to evaluate whether an IL-21-based MS therapy is required or is effective (claims 16-19). It is only through the disclosure of the instant application that one is taught that IL-10 is modulated during IL-21-based MS treatment, and thus it is only through the disclosure of the instant application that IL-10 is known to be a useful parameter to evaluate the desirability or efficacy of the IL-21-based MS treatment of claims 16-19. Therefore, Applicants respectfully submit that the combination of the '272 patent, the '549 application, Kawai, and Beebe would not provide the motivation or reasonable expectation of success required to arrive at: (1) Applicants' claims directed to treating, ameliorating, or preventing MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18 (claims 1-15 and 29-33); and (2) Applicants' claims that require evaluating an IL-10 parameter prior to or in response to administration of an IL-21 agonist for the treatment, prevention, or amelioration of MS or a symptom of MS associated with an IL-10 deficiency, increased IFN-γ, increased IL-1α, increased IL-2, increased IL-6, or increased IL-18 (claims 16-19).

In addition, the combination of the '272 patent, the '594 application, Kawai, and Beebe does not teach or suggest the limitations of claim 34. The '272 patent, the '549 application, and Kawai do not teach or suggest the nexus between IL-21 administration and treating, preventing, or ameliorating a disorder associated with an IL-10 deficiency. As discussed above, the '272 patent, the '594 application and Kawai all lack an indication that there is a nexus between IL-21 and IL-10. Further, while Beebe shows that an IL-10 increase is associated with MS treatment, Beebe also lacks a nexus between IL-21 and IL-10, and does not teach that an IL-21 agonist can be used to increase IL-10 levels. Thus, Applicants respectfully submit that claim 34 is not rendered obvious by the combination of the '272 patent, the '549 application, Kawai, and Beebe.

Claims 35-40 are also not rendered obvious by the combination of the cited references. As discussed above, the '272 application does not teach the link between IL-10 and IL-21, and does not teach administering an IL-21 agonist to a subject based on evaluating an IL-10 parameter. The '549 application and Kawai also do not teach the administration of IL-21 agonist to treat, prevent or ameliorate an IL-10 deficiency based on evaluating an IL-10 parameter. In addition, Beebe does not provide an association between IL-21 agonism and IL-10 levels. It is only through the disclosure of the instant application that one is taught that IL-10 is modulated by IL-21 administration, and thus only the disclosure of the instant application supports evaluating an IL-10 parameter and administering IL-21 to treat, prevent, or ameliorate an immunological disorder associated with an IL-10 deficiency based on the result of the IL-10 evaluation. Thus, claims 35-40 are not obvious over the combination of the '272 patent, the '549 application, Kawai, and Beebe.

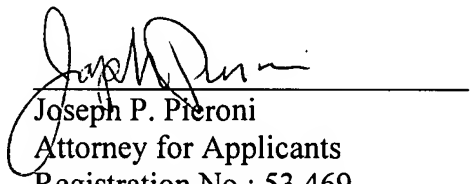
For at least these reasons, Applicants submit that claims 1-19 and 29-40 are neither disclosed nor suggested by the combination of the '272 patent, the '549 application, Kawai, and Beebe, and therefore respectfully request withdrawal of the obviousness-based rejections of claims 1-19 and 29-40.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that all of the Examiner's concerns and rejections have been answered and overcome, and that the subject matter of the presently claimed invention satisfies the requirements of 35 USC § 112 and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims are earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,



Joseph P. Pieroni
Attorney for Applicants
Registration No.: 53,469

FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, NY 10112-3801
Facsimile: (212) 218-2200

FCHS_WS 622210_2